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Health Policy Analysis

Assessing the Determinants of the Potential for Cost-Effectiveness Over Time: The Empirical Case of COPD

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ABSTRACT

Objectives: The objective of this study was to assess the potential for cost-effectiveness of new technologies for chronic obstructive pulmonary disease (COPD) over the period from 2001 to 2010. **Methods:** Lung function outcomes and drug prices were observed for a UK COPD population over the period from 2001 to 2010. Cost-effectiveness was assessed at regular intervals on the basis of an established cost-effectiveness model, and the maximum price a technology providing cure could achieve under the current cost-effectiveness rules was estimated. **Results:** The results of this study show that although the scope for clinical improvement in COPD was still considerable, during the 10 years studied, the potential for cost-effectiveness at each point in time was dependent on momentary market characteristics, such as the changing price of comparators and improvements in clinical

effectiveness. As a result, the analysis demonstrates that the future cost-effectiveness of a technology in development depends on the manner pricing and clinical effectiveness evolve throughout time.

Conclusions: Because any predictions will be short-lived and dependent on a number of uncertain factors, we conclude that producing accurate forecasts on the potential for cost-effectiveness of new therapies earlier during the development process is especially difficult under the current static cost-effectiveness framework.

Keywords: chronic obstructive pulmonary disease, cost-effectiveness, dynamic efficiency, pharmaceutical innovation, pharmaceutical policy, research and development.

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Introduction

Policy Context

The use of a decision-making framework based on cost-effectiveness is intended to achieve efficiency in drug spending by requiring an acceptable and affordable cost per unit of incremental effect for a new drug compared with existing therapies. However, with price variation over time due to market competition, the launch of new drugs, or the entrance of generic products [1,2], the incremental clinical effectiveness required for any drug to be cost-effective will change. In addition, the minimum price at which a company can launch a drug will be affected by a number of factors, such as the level and cost of regulation, the cost of capital, the size of the target population, the effective patent time before competitors reach the market, or the expected speed of market introduction [3–5].

Throughout the drug development process, candidates for new drugs are traditionally subjected to a rigorous portfolio assessment exercise. The most viable molecules are selected on the basis of a

range of factors such as the probability of regulatory success of the compound and clinical unmet need of the disease area and estimated return on investment. Because this process starts many years before the product enters the market, investment decisions in drug development are obviously surrounded by considerable uncertainty. If the expected returns accrued during the approximately 10 to 12 years of market exclusivity do not cover for the cost of development, the candidate drug will not be brought into development and resources will be placed elsewhere.

Contrasting with the dynamic nature of drug development, coverage and reimbursement decisions are increasingly based on a static notion of efficiency. In addition, contrarily to what happens in the drug development process, decisions are made at a single point in time. This has been suggested to cause a clash between the objectives of efficiently allocating available resources and fostering innovation in health care [6,7]. This study attempts to facilitate the discussion on the importance of cost-effectiveness in directing research in health care. It assesses how static cost-effectiveness rules may influence the dynamic environment of drug development, and examines the implications of

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taking static cost-effectiveness into account when developing drugs that will be valued and paid for.

Theoretical Background

This study tests empirically the assumptions underlying the framework proposed by Refoios Camejo et al. [6]. They suggest the existence of a physiologically defined clinical effectiveness ceiling for each disease area (E_D max), that is, a medical optimum from which health would not improve with the use of more health care. The maximum incremental clinical effectiveness (IE_d max) a new drug could attain over the effectiveness of existing standard care (E_c) if research and development resources were infinite is then defined by IE_d max = E_D max – E_c . Previous studies [8] have used a similar approach to assess the effect of price reduction over time on the size of the clinical benefit necessary for a new drug to be considered cost-effective.

Funding systems based on cost-effectiveness judge a new technology as cost-effective when the incremental monetary benefit provided is expected to be greater than the incremental costs incurred by adopting a new technology d over the available alternative c . This means that a new technology will be approved to be used in the health system if the net monetary benefit (NMB) achieved by funding is greater than zero; that is, $NMB_d = (E_d - E_c) \times L - (P_d - P_c) > 0$, where L represents a general cost-effectiveness threshold defining the acceptable cost per unit of incremental benefit and which is used to monetize health-related benefits. Because, within the context of a restricted budget, the adoption of a new technology necessarily implies the withdrawal of other (less cost-effective) technologies, this threshold is also said to represent the minimum opportunity cost of funding a new technology, that is, the benefits forgone by disinvesting in displaced technologies. The use of a single cost-effectiveness threshold is also suggested to allow the prioritization across diseases attempting to signal the areas in which research may be socially preferable.

In the case in which all the benefits of innovation accrue to the producer and producer surplus is maximized, NMB is set to equal zero and the price is set so that $(P_d - P_c) = (E_d - E_c) \times L$. In this way, the maximum price premium (P_D max) warranting a positive decision when reaching E_D max can be computed at each time point by taking into consideration the price of the comparator (P_c) and the clinical effectiveness of standard care (E_c). While P_c will greatly depend on the market characteristics and the shape of the innovation curve in that particular disease area, which, in turn, is dependent on the timing of new products entering the market and the magnitude of the clinical effectiveness increment they may bring, IE_d max will tend to decrease over time because of incremental innovation. At an extreme and under the investment rules present in the drug development process, if the minimum possible launch price for a product to be considered a viable investment with a positive net present value (P_d min) is expected to be higher than the maximum price allowed by IE_d max, no more investment will be made in research and development in that particular disease area.

In this context, chronic obstructive pulmonary disease (COPD) was selected to test the proposed framework empirically because the maximum clinical effectiveness possible (E_D max) for the technologies can be adequately defined through diagnostic tests or the nonexistence of exacerbation episodes; the level of clinical effectiveness of standard care (E_c) is expected to have a direct relationship with drug usage; and confounding factors eventually affecting the estimation of E_c are relatively small or can be controlled for.

The Case of COPD

COPD is a lung-related chronic condition lasting over the course of a patient's life that primarily affects people with a history of

smoking. Patients with COPD initially complain of breathlessness and may also have cough and increased sputum production, which tend to worsen over time. COPD is a major cause of morbidity and mortality worldwide, and current estimates of COPD prevalence in Europe are between 4% and 10% [9].

Lung function is essential for diagnosis and also an indicator of disease severity. Lung function impairment is measured through spirometry to derive values of forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1). Primary diagnosis criterion is a ratio of FEV_1 to FVC (FEV_1/FVC) smaller than 0.7 [10]. Lung function is often compared with the FEV_{1p} -predicted (FEV_{1p}) for a healthy person of similar age, gender, and body composition. The ratio between FEV_1 and FEV_{1p} , called forced expiratory volume in 1 second as a percentage of predicted ($FEV_1\%$), is used to determine COPD severity.

Since the late 1980s, a significant shift in the awareness of COPD has taken place. Previously, there was the widely held opinion that little could be done to treat patients with COPD, and spirometry was performed less frequently. The introduction of new pharmaceuticals together with other system-wide reforms, however, have been shown to bring benefits and contributed to change that view. In the particular case of the United Kingdom, COPD was included in the Quality & Outcomes Framework (QOF) incentive program for general practitioners introduced in 2004. Since then, a consistent move toward the routine collection of spirometry data in primary care became increasingly visible.

The treatment goal for COPD is now to prevent and control symptoms and reduce the frequency and severity of exacerbations [10]. Disease management is generally characterized by a stepwise approach depending on disease severity. More recently, newer treatments for COPD focus on an improved mode of action, for example, combining therapies into one inhaler and reducing the dosage frequency. Despite being a relatively recent area of research in its own right, the development of treatments for COPD has benefited from the knowledge acquired while researching medical technologies for other respiratory conditions. This is significant because innovation in treating respiratory diseases has also been achieved through the development of more efficient delivery systems.

Study Objectives and Scope

The objective of this study was to estimate the potential for cost-effectiveness of new technologies for COPD over time and assess how that is influenced by the evolution of clinical effectiveness, and the pricing pattern of available medical alternatives. The study illustrates how the real-life clinical effectiveness of existing standard care in the population being managed for COPD has changed over time. It subsequently uses the price of pharmaceutical standard care to estimate the maximum cost-effectiveness possible at different points in time and the higher price that a new technology providing cure could achieve under current cost-effectiveness rules when entering the market.

Rather than intending to test the clinical and cost-effectiveness of any particular technology, this study aimed at providing an overall medium-/long-term perspective of the evolving potential for cost-effectiveness in COPD. We then discuss the potential impact of these readings on the development of further technologies.

Methods

Lung function outcomes and prices of available drugs were observed between 2001 and 2010, and cost-effectiveness was estimated at yearly time points to reflect the prevailing prices and gap for clinical improvement. Extensive literature is available on the efficacy of available drugs in managing COPD within

clinical trials. Effectiveness in practice, however, often differs from controlled trials because of patient heterogeneity, lack of patient compliance, variations in clinical management, and changing demographics or health habits. Hence, to estimate the real-life clinical effectiveness of existing standard care (E_c), the analysis used real-life clinical data covering a 10-year observation period.

Medical records of patients identified as being managed for COPD were compiled, and spirometry test data and COPD-related exacerbations information were collected. Population outcomes were derived and residual unmet clinical need (IE_d max) was computed for each year of the analysis. In addition, prevailing prices for drugs used to manage COPD were collected from 2001 to 2010 and the average yearly price of existing standard care was estimated by computing the weighted average of drugs used to manage COPD in each year. Finally, the potential for cost-effectiveness of new technologies was estimated by using a cost-effectiveness model. We present the methods for each of these analytical steps separately below.

Data Sources

Clinical effectiveness

Data were extracted from the Clinical Practice Research Database (CPRD). The CPRD is an anonymized database of medical records of general practitioners in the United Kingdom. Data collection began in 1987, and the database contains data from more than 600 practices based throughout the United Kingdom, providing information on 12.5 million patients, of which 5 million are currently active. The CPRD population is considered to be representative of the UK population, and data held in the CPRD include patient, practice, and laboratory information.

In this study, extracted data included spirometry measurements and other variables useful to characterize the population (gender, age, height, smoking status, prescribing history, and hospitalization episodes). Exacerbations were identified by the recording of COPD exacerbation or by any emergency admissions related to COPD (*International Classification of Diseases* version 10 codes J40–J44 and J47 [11]) through Hospital Episodes Statistics data. In addition, exacerbations were recognized by the prescription of oral steroids or short-term antibiotics with an inclusion code relating to a lower respiratory tract infection.

Price of existing pharmacotherapy standard care

Pricing and market information was collected from Prescription Cost Analysis (PCA) data [12]. PCA data are based on prescriptions in England that are sent to the National Health Service Prescription Services for payment and cover all prescriptions dispensed in the community, therefore, representing the great majority of pharmaceutical expenditure in the National Health Service. The data set comprised all generic and nongeneric drugs used in COPD (i.e., included in the British National Formulary's paragraphs 3.1.1.1—Selective Beta(2)-Agonists, 3.1.2—Antimuscarinic Bronchodilators, 3.1.3—Theophylline, and 3.2—Corticosteroids (Respiratory) [13]) with reported sales in the UK market between 2001 and 2010. Retail pricing (representing the yearly average cost of the drug before discounts and excluding any dispensing fees) was available at the product level. Product-specific market yearly data (such as quantity of presentations sold, number of molecules available, and number of generic products available) were also collected from PCA.

Analysis

Clinical effectiveness

The baseline population included all newly diagnosed COPD patients present in the CPRD database who had been prescribed

bronchodilators in the period 2001 to 2010. Patients with a recorded diagnosis of COPD were included in the study. In addition, patients older than 35 years who had been hospitalized with a primary or secondary diagnosis of chronic bronchitis, emphysema, or chronic airway obstructions were also included. Patients older than 45 years at their first dispensing for bronchodilators were included, provided they had no previous record of asthma diagnosis or any asthma-related episodes.

The cohort entry date was defined as the date of the first bronchodilator drug prescription, and patients were required to have at least 6 months of bronchodilator-free history before cohort entry date. Patients with spirometry test results showing a $FEV_1\%$ of 80% or more or FEV_1/FVC of 70% or more at diagnosis were excluded. In addition, patients without a recorded test result within 15 months after cohort entry date were also excluded. In the case FEV_1 or $FEV_1\%$ values were not recorded or FEV_1 could not be computed by using existent values of FEV_1/FVC and FVC , the patient was excluded from the analysis.

The clinical effectiveness of existing standard care (E_c) was represented by $FEV_1\%$. $FEV_1\%$ was estimated annually during the study time period by using patients' first spirometry test result available within 15 months after the cohort entry date. When not directly recorded in the patient files, $FEV_1\%$ was computed by dividing FEV_1 by FEV_1p , with FEV_1p being estimated by using the predictive equations derived by Starkie [14]:

$$FEV_1(L) \text{ in men} = -1.859 - 0.029 \times \text{age (years)} + 0.037 \times \text{height (cm)}$$

$$FEV_1(L) \text{ in women} = -0.225 - 0.029 \times \text{age (years)} + 0.024 \times \text{height (cm)}$$

To test for possible variation in patient characteristics over time, age, height, and gender (condensed in the values of FEV_1p) at the time of cohort entry were compared across years by using one-way analysis of variance. Patient characteristics were also compared before and after the introduction of the QOF (i.e., 2004) by using a standard univariate *t* test. When data were not available for any of the demographic variables, multiple imputations was used to deal with missing data.

The calendar year in which the test had been taken (ranging from 2001 to 2010) was defined as the index date and used to estimate the population E_c in the year in question. As per definition, E_d max reflected the point at which all mortality and morbidity associated with COPD was eliminated. This was assumed to occur when all patients achieved the treatment goal, defined in the study by $FEV_1\%$ of 80% or more and a 1-year absence of exacerbations and COPD-related hospitalizations. In other disease areas, treatment goals have changed over time; however, this is not the case for COPD because the threshold of spirometry values required for diagnosis has not changed significantly during the study period.

The individual increase needed in $FEV_1\%$ for a patient to reach the recommended treatment target was defined as IE_d max, and estimated by $IE_d \text{ max} = E_d \text{ max} - E_c$ [6]. The residual unmet need, IE_d max, was then calculated as the mean of those values in each calendar year. As a sensitivity analysis, the median population IE_d max was also computed for each year. All analyses were conducted by using STATA 11.

Price of existing pharmacotherapy standard care

Drugs for COPD are normally available in the form of one-dose solid preparations (pills, capsules, or tablets) and in multidose containers including aerosols or dry powder to be used in inhaling devices. To determine the yearly price of standard care, an indicator consisting of the volume-weighted average price per item prescribed (P/pack) was used. This indicator was preferred to price per unit because the PCA's coding of unit results in a single pill being equivalent to a multidose inhaler independently of how many administrations it allows. Volume-weighted P/pack

Table 1 – Studied population characteristics at cohort entry including gender, age, height, and forced expiratory volume in 1 second predicted for a healthy person of the same age and body composition (FEV_{1p}).

Year	n	Gender (% male)	Mean ± SD		
			Age (y)	Height (cm)	FEV _{1p} (L)
2001	75	60.00	71 ± 9	167 ± 8	2.08 ± 0.54
2002	130	63.85	70 ± 10	168 ± 9	2.15 ± 0.58
2003	262	67.28	71 ± 10	169 ± 9	2.20 ± 0.56
2004	1,039	62.28	72 ± 10	168 ± 9	2.09 ± 0.59
2005	1,070	63.36	72 ± 10	168 ± 10	2.11 ± 0.61
2006	1,278	63.93	72 ± 11	169 ± 10	2.14 ± 0.62
2007	1,753	63.30	72 ± 11	169 ± 10	2.13 ± 0.60
2008	2,038	61.86	72 ± 11	168 ± 9	2.12 ± 0.59
2009	2,770	62.58	70 ± 11	169 ± 9	2.17 ± 0.60
2010	6,879	64.54	70 ± 10	169 ± 9	2.22 ± 0.59
Total	17,294	63.54	71 ± 10	169 ± 10	2.17 ± 0.58

was computed for each molecule by using the sales of all presentations available in each 1-year time period. Volume-weighted average *P*/pack was then computed for each subclass and for the whole therapeutic area (*P_c*). *P*/pack was back and forward dated by using the non-health-specific consumer price index to account for inflation [15].

Potential for cost-effectiveness

The potential for cost-effectiveness was analyzed by testing the maximum price a new drug could achieve under the current cost-effectiveness rules. Using the cost-utility economic model developed by Starkie [14], the lifetime health-related quality-of-life benefits and cost savings associated with achieving *E_D* max were estimated. The model followed a conceptual regression-based framework and allowed interdependence to exist between the different components of COPD. Thus, an increase in FEV_{1p} was converted into lung function improvement and reflected in symptoms, exacerbations, survival, health care costs, and utility. The model followed the base case advocated by the National Institute for Health and Clinical Excellence in its guide to the methods of technology appraisal [16].

The cost-utility model was used to predict quality-adjusted life-year (QALY) and costs associated with existing standard care by using the yearly population FEV_{1p} and the weighted-average *P*/pack. The potential QALY gained for a treatment achieving *E_D* max was estimated for each year; and the maximum price achievable by *IE_d* max (*P_D* max) in light of the National Institute for Health and Clinical Excellence's £20,000 per QALY cost-effectiveness threshold was computed. The demographic characteristics (age and height) of the modeled cohort were defined on the basis of the average of the values observed across years. To accommodate potential severity imbalances across gender and age, all analyses were completed separately by using values for female and male patients and the overall population results were adjusted according to their proportion in each year. All calculations used in estimating cost-effectiveness were conducted by using prices and costs adjusted to 2006 prices by using the non-health-specific consumer price index [15].

Results

Clinical Effectiveness

Population characteristics

Out of the 210,700 patients identified as COPD patients from 2001 to 2010, 46,426 patients had linked spirometry data. Of these,

17,294 patients met the inclusion criteria of having a test result within 15 months after the cohort entry date and were included in the analysis. Population characteristics at cohort entry can be seen in Table 1.

Table 1 shows that the number of people with spirometry measures has rapidly increased over time, particularly after 2004. However, this trend did not cause much disparity in terms of demographic baseline characteristics: the hypothesis that the mean of FEV_{1p} values (used as a composite measure of gender, age, and height at baseline) varied across the years was rejected (*P* = 0.461). In addition, the hypothesis that mean FEV_{1p} values before and after the introduction of the QOF (i.e., before and after 2004) were different was also rejected and deemed highly insignificant (*P* = 0.853). In exploratory analyses by gender, mean FEV_{1p} values across years for female patients (mean = 1.59 ± 0.35) were found to be significantly lower (*P* = 0.000) than the mean FEV_{1p} values for the male population (mean = 2.51 ± 0.41).

FEV_{1p} as a percentage of predicted

Mean population FEV_{1p} measured within 15 months of cohort entry was shown to increase fairly steadily, starting close to 51% in 2001 and increasing to approximately 59% in 2010 (Fig. 1). One-way analysis of variance confirmed that the difference across the yearly mean FEV_{1p} values was statistically significant (*P* = 0.000).

The observed trend of steadily increasing FEV_{1p}, as shown in Figure 1, was maintained throughout the study period while *IE_d* max decreased throughout the study period; however, FEV_{1p} values were still some way from the clinical target of 80%, which means that there was still substantial potential for innovation in this disease area.

Price of Existing Pharmacotherapy Standard Care

During 2001 to 2010, the market for COPD drugs saw the entrance of several new therapies and the loss of exclusivity for older molecules. In total, 14 molecules, in several combinations and pharmaceutical forms, were available at some point during the period studied. Because the effectiveness of treatment tends to be linked with the emergence of new molecules, as well as with innovative delivery systems, the weighted average *P*/pack naturally followed the paced introduction of these innovations (Fig. 2) and generally increased over the study period.

The weighted average nominal *P*/pack varied throughout the decade analyzed, fluctuating noticeably and rising 44% overall from £13.46 per pack in 2001 to £19.61 per pack in 2010 in 2006 pound sterling. The corticosteroid subclass, which included the

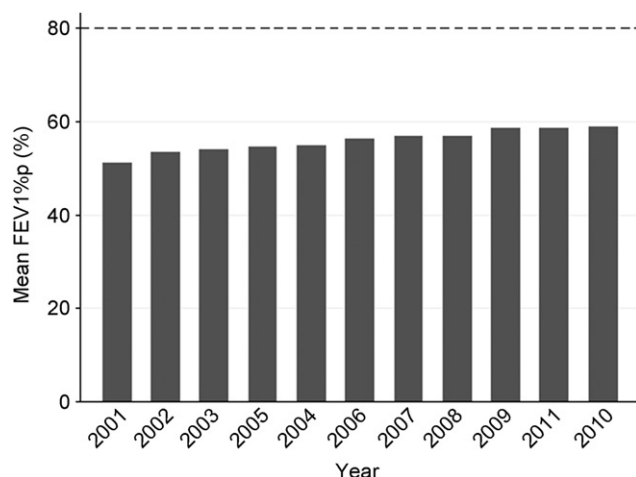


Fig. 1 – Mean forced expiratory volume in 1 second as a percentage of predicted (FEV₁%p) in patients being managed for COPD across the study period. Cure is assumed to be achieved at the 80% level of FEV₁%p and is represented by the reference line. Yearly IE_d max is represented by the gap between the top of each bar (showing the yearly mean value of FEV₁%p) and the mentioned reference line. COPD, chronic obstructive pulmonary disease.

combination of corticosteroids and selective beta(2)-agonists molecules in new delivery systems, commanded the highest prices. Real prices in this subclass (as in the selective beta(2)-agonists subclass), however, showed a significant decreasing trend. The most striking observation was related to the introduction of a new molecule (i.e., tiotropium in 2002 in the antimuscarinic bronchodilators subclass) and its gradual uptake, which caused a noticeable increase in the average P/pack. Apart from the case of salmeterol in 2007 in the selective beta(2)-agonists subclass, loss of exclusivity for older molecules did not appear to particularly affect average class P/pack.

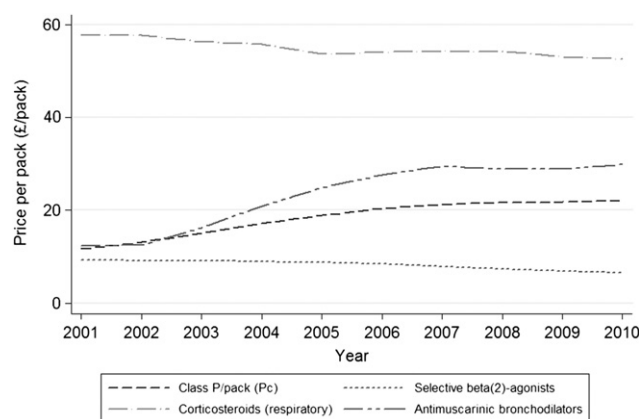


Fig. 2 – Real (in 2006 sterling pound) weighted-average price per pack (P/pack) for drugs used in COPD between 2001 and 2010 by therapeutic subclass and averaged across subclasses—Class P/pack (P_c). COPD, chronic obstructive pulmonary disease.

Potential for Cost-Effectiveness

In the period between 2001 and 2010, the economic model predicted that 0.28 QALYs were gained per patient because of the improvement in the management of COPD. This meant that the absolute potential for incremental clinical effectiveness measured in terms of health-related quality of life decreased approximately 25% from 1.09 QALY to 0.81 QALY (Table 2).

Consequently, the maximum possible price for a technology that increased FEV₁%p to 80% and consequently eliminated any mortality and morbidity associated with COPD was found to decrease by 12.75% between 2001 and 2010 (Table 2). Nevertheless, the price of a treatment that cured COPD was still considerably higher than the average price of existing standard care, which suggests that there is still scope to invest in the development of new treatments for COPD.

The potential for cost-effectiveness estimated through the model depended noticeably on the level of effectiveness of standard care and the prices of comparators. While the former presented a somewhat linear decreasing trend, the latter was shown to be susceptible to greater variations. As a consequence, P_D max did not follow a well-defined pattern and the magnitude of the potential for cost-effectiveness was shown to be momentary and dependent mostly on the transient market characteristics.

Sensitivity analysis around the modeled cohort, using alternative estimates for age and height, did not affect the main results. When P_c was reduced by 75% (to levels that have been assumed to be those of a competitive market price where only generic products were available), P_D max in 2010 decreased from £51.13 to £38.47. This means that the maximum possible price for a “curative” technology decreased from 2.31 to 1.76 times P_c.

Discussion

This study showed that the clinical effectiveness of standard (pharmaceutical and nonpharmaceutical) disease management has improved over time, with average FEV₁%p increasing from 51% in 2001 to approximately 59% in 2010. This represented a gain of 0.28 QALYs, which was approximately 25% of the total clinical benefit possible to achieve. The results show that the average price of drugs used in COPD varied considerably across the 10 years studied, and increased nearly 44% overall, reflecting the introduction of new chemical entities and of new delivery systems. As expected, all these factors played a role in determining the potential for cost-effectiveness possible for new drugs entering the market at different points in time. As a result, the maximum price achievable under current cost-effectiveness rules for a drug providing cure decreased by approximately 13%. Although a decreasing trend was noted overall, however, the predicted potential for cost-effectiveness fluctuated from year to year because of market variations during the period studied.

The 10-year observation period of real-life data provided a comprehensive description of the evolution of disease management and the pricing patterns of available treatments. As with any empirical study relying on observational data, however, the results from these analyses should be interpreted with caution because other unobserved factors may be associated with our findings. The fact that spirometry test results had to be available for a patient to be included in the study may have led to the inclusion of more severe patients into the study, because more severe patients are more likely to have more measurements recorded.

Also, taking into consideration that these tend to be lifetime prescriptions with a fairly low compliance, a single observation

Table 2 – Values of maximum incremental clinical effectiveness possible (IE_d max) and price of existing standard care (P_c) used as inputs in the base-case analysis; incremental QALY, and costs associated with a new treatment achieving IE_d max; and the maximum price possible for a drug achieving cure (P_D max) in line with an ICER of £20,000 per QALY.

Year	Mean IE_d max (FEV ₁ %p in %)	P_c (P/pack) (2006 £s)	Incremental QALY	P_D max (P/pack) (2006 £s)
2001	28.85	13.64	1.09	58.74
2002	26.52	15.00	0.99	55.46
2003	25.95	16.98	0.97	56.24
2004	25.30	18.78	0.96	57.20
2005	25.58	20.05	0.96	58.52
2006	23.85	20.40	0.90	56.07
2007	23.34	20.38	0.89	55.45
2008	23.30	19.99	0.88	55.17
2009	21.52	20.17	0.82	52.36
2010	21.27	19.61	0.81	51.25

Note: Costs in the model included drug acquisition costs and other costs incurred in managing the disease, for example, costs of COPD-related clinical events such as exacerbations.

COPD, chronic obstructive pulmonary disease; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

point may have influenced the estimation of E_c . Longer follow-up and delayed measurement (e.g., use of FEV₁ test results 2 years after cohort entry date), however, would have exceedingly reduced the sample. Management and awareness of COPD has changed considerably over the last 20 years and the number of patients followed up in the study increased throughout the years. This may have resulted in a relative increase in earlier diagnosis of potentially less severe patients in the latter years of the study. Nevertheless, no statistically significant difference was found between the baselines characteristics of patients included across the years and before and after 2004, the year the QOF was introduced.

In addition to a better understanding of the pathophysiology of the disease and better disease management strategies, the launch of new medical technologies in the last 10 years has steadily improved the standard of treatment available. Given the scope for incremental clinical effectiveness, however, it seems apparent that disease management in COPD, although improving over time, is not as advanced as in other areas. Investment in this particular disease is relatively recent, and it can be argued that these are early steps and that the innovation curve is still at its infancy. This scenario is, however, expected to change soon because several new products are anticipated to enter the market in the near future taking the management of COPD a step further.

Overall, price variations of standard care comparators were not linear over time. This resulted both from the introduction of new technologies and from the constant modification of the standard treatment mix because of the progressive uptake of newer technologies. It is also apparent that the generic market is not truly developed in COPD and that the extent of potential price decreases due to generic entry was smaller than normally experienced in other disease areas. This was probably because some of the highly used drugs and inhalers are still under patent protection. When loss of exclusivity occurred, older molecules appeared to be replaced by newer technologies and the average price of available technologies was not significantly affected. In addition, the dual-innovation system based both on chemical entities and on drug delivery devices may create an intellectual property picture that is more intricate than that of a normal market.

In this analysis, the standard level of care was estimated by measuring the effectiveness in the whole disease spectrum. However, cost-effectiveness of a new technology is normally judged on the basis of clinical trials efficacy. How that efficacy

translates in practice into effectiveness is dependent on the efficiency of the health system itself, which the developer cannot control. In this study, it was assumed that a new technology would deliver its full potential to provide cure, which presumes that the system would also be optimized. Particular interventions or tools such as improved diagnostic tests can sometimes work as catalysts for the necessary system innovation. Hence, there is a rationale for individual cost-effectiveness to be considered under a more holistic approach recognizing the importance of the health care delivery chain in working toward the optimal technology introduction and usage.

As expected, the potential for cost-effectiveness suffered a reduction overall in the 10 years studied. The study, however, shows that it remained high during the period studied, and the fact that the maximum price obtainable for a treatment that eventually cured COPD was considerably higher than the average cost of available drugs suggests that the incentive to invest in COPD was present throughout. This is mostly due to the increase observed in the price of comparators, which prevented a further erosion of P_D max. However, whilst this happened for COPD with its particular market structure, this has been found not to be the case in other disease areas where price erosion occurred and considerably diminished the potential for cost effectiveness [8]. Hence, as postulated by Refoios Camejo et al. [6], these results, in conjunction with previous studies, illustrate that the factors influencing the prediction of cost-effectiveness of new technologies are highly dependent on the rate of incremental clinical advancements and the pricing patterns in each particular disease area.

Because of the nature of drug research and the regulatory processes in place, the conditions of the market need to be predicted at early stages of development 10 or more years before they occur. This is naturally difficult and challenges the allocation of research and development funding. Early cost-effectiveness prediction is suggested to be able to play a role in reducing investment uncertainty by signaling the payers' willingness to pay for a particular health benefit. The prediction of a technology's future cost-effectiveness, however, is not straightforward because the evolution of the market depends not only on the future performance of the technology being developed but also on the success of competitor technologies in development elsewhere at the same time.

The results from this study corroborate this idea and suggest that the variation in the pricing patterns does not necessarily

reflect the changes in clinical effectiveness achieved over time. Prices of available technologies will depend on the particular characteristics of the pharmaceutical market, such as the number of competitors or the degree and pace of generic introduction. In addition, clinical effectiveness within a disease area evolves with many factors such as the introduction of new technologies, the development of new means of diagnostic, or the wider adherence to clinical guidelines. When cost-effectiveness potential is momentary and dependent on the transient conditions of the market, a positive decision on whether to fund a technology based on cost-effectiveness may end up being highly dependent on the particular timing of the appraisal. This dynamic nature is present throughout the product's lifecycle and, being different across diseases, will be difficult to capture at a single point of market entry when price is decided upon by using a general cost-effectiveness threshold.

This introduces uncertainty into the development process and consequently results in higher costs of development. In practice, it may produce an inefficient allocation of research and development resources; that is, either overinvestment will take place or affordable research will be foregone with investment being short of the societal optimal. Ultimately, considering that pharmaceutical innovation is path dependent, this increased uncertainty surrounding the cost-effectiveness potential may result in the complete withdrawal from research within a particular disease area. In addition, because different disease areas are constantly competing for research and development funds, any influence cost-effectiveness might have in directing drug development to a particular health condition may be distorted.

Cost-effectiveness still has an essential role to play in signaling the health systems' willingness to pay and in directing research to the areas society values most.

However, this can be achieved only if the current decision-making framework is adapted to incorporate the dynamic nature of drug development and the specificities of the disease area. Although some reimbursement bodies may already consider some of these concerns in the appraisal stage of the decision-making process by allowing higher thresholds when certain requirements are met [16–18], a more structured approach may be necessary. Suggestions on how to tackle this issue explicitly may, for instance, entail the designation of silo disease-specific budgets based on the societal preferences for treating particular diseases, and disease-specific thresholds defined to represent the shadow price of such budgets. Alternatively, two budgetary components could be defined separately: the first would be dependent on the total health care budget with a threshold defined on the basis of the foregone benefit of displacing other technologies elsewhere in the health system and the second component would imply the definition of a global innovation budget, subdefined by disease area. In any case, further research and a wider debate will be necessary to devise a system that allows cost-effectiveness to efficiently direct investment in pharmaceutical research.

Conclusions

The results of this study show that despite the noticeable advancement in managing COPD in recent years, clinical unmet need is substantial and there is significant scope for clinical improvement in this disease area. The potential for future cost-effectiveness, as judged by current cost-effectiveness rules, decreased but it is still considerable. This was found to be the case because innovation in COPD is still at its infancy and, contrarily to what was seen in other disease areas, the impact of generic entry had not had a marked effect on the price of existing comparators. The analysis further suggests that during the 10 years studied, the potential for cost-effectiveness of new therapies was momentary, dependent on the

transient market characteristics and specific to each disease area, and so any predictions of future cost-effectiveness are naturally short-lived. As a result, under the current static cost-effectiveness framework, it is especially difficult to produce accurate estimates of the potential for cost-effectiveness of new therapies earlier in the development process.

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Supplemental Materials

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